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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/770,002	01/25/2001	Peter Lloyd Amlot	4-30583A	5207

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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
05/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/770,002	AMLOT ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,5,8,13 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *4,5,8,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 4, 5, 8, 13, and 14 are being acted upon.

2. Applicant's amendment and remarks, filed 2/05/07, are acknowledged.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 4, 5, 8, 13, and 14, stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

As set forth previously, There is insufficient written description to show that Applicant was in possession of a CD25 binding molecule, other than basiliximab. The specification discloses that "By "CD25 binding molecule" is meant any molecule capable of binding to the CD25 antigen either alone or associated with other molecules to form high affinity IL-2 receptors." Said definition must clearly be considered to encompass a large genus that might include peptides, proteins, and mimitopes, etc. However, the specification discloses just a single antibody (basiliximab) capable of binding CD25. Accordingly, one of skill in the art must conclude then that the specification fails to disclose a representative number of species to describe the claimed genus.

The claims were subsequently amended to recite a method employing the CDRs of the basiliximab antibody.

As then set forth, It is the Examiner's position that, as Applicant has disclosed only one embodiment of the antibody of the claims, using only said single embodiment, Applicant cannot accurately estimate the size of the antibody genus of which said antibody is a species. Additionally, chimeric antibodies consist of more than just a collection of amino acid fragments, i.e., CDRs. Antibodies comprise complex three dimensional structures in which the CDRs must fit in precise three dimensional space to create an antibody specific for any particular ligand. It is well-known in the immunological arts that the substituting of CDRs into a random framework is highly unlikely to result in an antibody of the same specificity as that of the antibody from which the CDRs were

derived. Chimeric antibodies are actually constructed by trial and error starting with a framework that appears to resemble that from which the CDRs were derived. Accordingly, a written description that consists only of the CDR regions is inadequate to describe the CD25 binding molecule of the instant claims.

The application discloses just a single embodiment of the antibody employed in the claims, but said embodiment, coupled with the level of skill in the art, would lead one skilled in the art to recognize that Applicant was in possession of the claimed method. Applicant introduces a number of references in support of the argument that additional antibodies encompassed by the claimed method could be produced.

It is the Examiner's position that Applicant's arguments would be more appropriate for a rejection based on lack of enablement. Note, however, that no rejection for lack of enablement has been made. The possibility that an invention might be produced without undue experimentation does not mean that said invention has also been adequately described. Also note that at least two of the cited references, U.S. Patent 6,180,370 and Vaswani et al., were published *after* the priority date of the instant application and thus demonstrate nothing regarding the state of the art at the time of the instant invention.

In the instant case, Claims 4, 5, 14, and 15 describe a generic antibody by just 3 of 6 CDR regions and no framework. That comprises just 30 amino acids, or less than 2.3% of the approximately 1320 amino acids of a complete antibody. Claims 12 and 13 recite an additional 3 CDRs, 24 amino acids, such that a total of 54 amino acids, or less than 4.1% of the approximately 1320 amino acids of a complete antibody are described. It remains the Examiner's position that this comprises an inadequate description of the generic antibody employed in the method of the instant claims.

Applicant's arguments filed 2/05/07 have been fully considered but they are not persuasive. Applicant argues that the instant amendment overcomes the rejection.

It is noted that independent Claim 4 now incorporates the limitations of canceled Claim 12. As set forth above, Claim 12 was previously rejected for inadequate written description. Accordingly, the rejection has been maintained for the reasons of record.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c)and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 4, 5, 8, 13, and 14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 89/09622 (IDS, of record) in view of Kovarik et al. (1997, of record).

As set forth previously, WO 89/09622 teaches a method of treating rheumatoid arthritis (RA) comprising administering an effective amount of a CD25 binding molecule. The reference further teaches the coadministration of a further substance effective in the treatment of RA (e.g., methotrexate) (see particularly page 12).

The reference differs from the claimed invention in that it does not teach the administration of a CD25 binding molecule comprising a CDR1, CDR2, and CDR3 having the amino acid sequences Arg-Tyr-Trp-Met-His, Ala-Ile-Tyr-Pro-Gly-Asn-Ser-Asp-Thr-Ser-Tyr-Asn-Gln-Lys-Phe-Glu-Gly, and Asp-Tyr-Gly-Tyr-Tyr-Phe-Asp-Phe, respectively, nor direct equivalents.

Kovarik et al. teaches a CD25 binding molecule comprising a CDR1, CDR2, and CDR3 having the amino acid sequences Arg-Tyr-Trp-Met-His, Ala-Ile-Tyr-Pro-Gly-Asn-Ser-Asp-Thr-Ser-Tyr-Asn-Gln-Lys-Phe-Glu-Gly, and Asp-Tyr-Gly-Tyr-Tyr-Phe-Asp-Phe, respectively, (basiliximab) (see particularly page 1702, column 1, *Study treatments*). The reference also teaches that serum concentrations of basiliximab sufficient to saturate IL-2 receptors were achievable (see particularly *Pharmacokinetics*, Tables 1 and 2)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform a method of treating RA comprising administering an effective amount of a CD25 binding molecule, with or without coadministration of a further substance effective in the treatment of RA, as taught by WO 89/09622, employing basiliximab, as taught by Kovarik et al. One of ordinary skill in the art at the time the invention was made would have been motivated to use basiliximab as the CD25 binding agent because basiliximab was a well-known CD25 binding agent and it was known that serum concentrations of basiliximab sufficient to saturate IL-2 receptors were achievable, as taught by Kovarik et al. Note that the saturation of IL-2 receptors is the mechanism by which the treatment of the instant claims would be expected to functions.

It is the Examiner's position that if the '622 document taught that the specific antibodies recited in amended independent claim 4 (basiliximab) could be utilized to treat rheumatoid arthritis, the instant rejection would have been under 102(b). Because the reference did not teach the use of the single antibody of the instant specification (basiliximab) a secondary reference was required and

the rejection was made under 103 for obviousness. The reference does teach that "The present invention provides novel compositions useful in the treatment of T-cell mediated human disorders, the compositions containing a chimeric antibody specifically capable of binding to human IL-2 receptors, such as at the epitope bound by the anti-Tac monoclonal antibody. The IL-2 chimeric antibody can have two pairs of light chain/heavy chain complexes, wherein at least one pair has chains comprising mouse variable regions joined with human constant region segments, with or without naturally-associated J and D segments" (page 3) and further teaches RA as one such disease. In other words, the reference teaches the use of a chimeric anti-IL2 receptor antibody for the treatment of RA. Kovarik et al. teaches the chimeric anti-IL2 receptor antibody basiliximab which comprises the CDRs of the instant claims. Accordingly the combined references need comprise nothing more than the substitution of obvious equivalents for a proper obviousness type rejection. However, the Kovarik et al. reference teaches more. It also teaches that basiliximab can achieve IL2 receptor saturation and that the antibody is well tolerated, thus basiliximab could be considered to be not just an equivalent of the antibody of the '622 document, but a *preferred* substitution for said antibody.

Applicant's arguments filed 2/05/07 have been fully considered but they are not persuasive. Applicant appears to attempt to discredit the primary reference by arguing that it contains no *in vivo* data.

Applicant's argument seems incredible given the fact that the instant specification itself discloses no *in vivo* data.

The specification's *entire* teaching regarding the use of the antibody of the instant claims for the treatment of RA is as follows:

> Example 1:
> Basiliximab is administered intravenously at a dose of 60 mg on Day 0, 40 mg on Day 28 and 40 mg on Day 56. Patients are evaluated at Weeks 2, 4, 6, 8, 10 and 12 for safety, efficacy and disease outcome.
> The primary efficacy outcome measure is the attainment of ACR (American College of Rheumatology) criteria for improvement of rheumatoid arthritis at Week 12. ACR (20) criteria defines improvement as 20% improvement in the number of tender and swollen joints, in addition to 20% improvement in at least three of five variables (degree of disability, HAQ (Health Activity Questionnaire); patient global assessment; physician global assessment; pain and C-reactive protein).
> Patients receiving basiliximab show an amelioration of the symptoms as compared to patients receiving placebo.
> Example 2:
> Basiliximab is administered intravenously at a dose of 0.02 mg on Day 0, 0.2 mg on Day 4, 2 mg on Day 8, 20 mg on Day 12, 40 mg on Day 19 and 60 mg on Day 26. Patients are evaluated at Weeks 2, 4, 6, 8, 10 and 12 for safety, efficacy and disease outcome as in Example 1.
> Patients receiving basiliximab show an amelioration of the symptoms as compared to patients receiving placebo.

Should Applicant's argument be found persuasive, a rejection under the first paragraph of 35 U.S.C. 112 for lack of enablement would clearly be required. As set forth in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art "would accept without question" an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

> "As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Applicant has submitted seven abstracts in support of their position.

A review of the abstracts reveals that none of them teach that an anti-CD25 antibody would not be expected to provide treatment for RA. Indeed, none of the abstracts consider the use of an anti-CD25 antibody for any treatment. Thus, it remains the Examiner's position that the use of a well-known immunosuppressive drug (Basiliximab) for the treatment of a well-known autoimmune disease (RA) would have been obvious to the skilled artisan at the time of the invention.

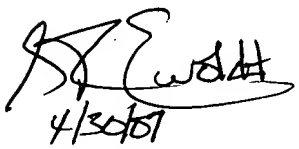
8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

11. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.



4/30/07

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